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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,959	04/04/2006	Paul D. Rennert	13751-055US1 A184 US	5124

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,959	RENNERT, PAUL D.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-54* is/are pending in the application.

4a) Of the above claim(s) *43,44 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 42-54 are pending.

2. Applicant's election without traverse of Group I, claims 42-47 (now 42 and 45-47) directed to a method of treating an autoimmune disease in a subject comprising administering a composition comprising an antibody or antigen-binding fragment thereof that binds to KIM-1 and the inflammatory bowel disease as the species ,filed on 1/25/08, is acknowledged.

3. Claims 43-44 and 48-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 42 and 45-47 are under examination as they read on a method of treating an autoimmune disease in a subject comprising administering a composition comprising an antibody or antigen-binding fragment thereof that binds to KIM-1 and the inflammatory bowel disease as the species.

5. Applicant's IDS, filed 5/12/06, is acknowledged.

6. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figure 1, on page 5, line 22 has describe two splice variants of the human KIM-1 polypeptides (334 and 359 amino acids) that each must have a sequence identifier. It is noted that Fig. 1 indicates that the listed sequences is SEQ ID NO: 1, however the sequence listing list SEQ ID NO: 1 as 518 amino acid sequence. Moreover, the specification on pages 31-34 disclosed 5 sequences that each must have a sequence identifier. Correction is required.

7. Figure 1 is objected to because the listed sequence is not SEQ ID NO: 1. Correction is required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 42 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating inflammatory bowel disease with KIM-1-Ig fusion protein, does not reasonably provide enablement for a method of treating an autoimmune disease/immunological disorder in a subject comprising administering an antibody or antigen-binding fragment thereof that binds to KIM-1, wherein the disorder/disease is inflammatory bowel disease in claims 42 and 45-47. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The claimed method is drawn to administering anti-KIM-1 antibodies to treat an autoimmune disease/immunological disorder including inflammatory bowel disease (IBD). The claimed anti-KIM-1 antibodies would encompass antibodies that act as agonists or antagonists of KIM-1 function. The specification on page 47, line 8-10, discloses that KIM-1 modulation could influence the production of proinflammatory mediators such as IFNγ. Figure 8 summarizes the effect of 5 anti-mouse KIM-1mAbs on IFNγ production in mouse MLR cultures. The specification on page 6, lines 16-17 and page 45, lines 19-20 discloses that treatment of the cultures with mAbs 3A2 and 1H9 during incubation significantly reduced the level of IFNγ secreted into the supernatant. Similarly, Figure 12A summarizes the effect of 6 anti-human KIM-1 mAbs on the IFNγ production in human MLR cultures. The specification on page 7, lines 6-8 and page 46, lines 23-24 discloses that treatment of the cultures with mAbs AUF1 and AKG7 during incubation significantly reduced the level of IFNγ secreted into the supernatant. It seems unlikely that any antibody that binds KIM-1 would be capable of reducing the level of IFNγ secretion, as broadly claimed. The specification on lines 10-13 discloses that it was hypothesized that the KIM-1-Ig fusion protein was acting by interrupting the interaction of one or more ligands with KIM-1 expressed on cells such as activated lymphocytes or the immune cells. However, Xiao *et al* (JEM, 204(7):1691-1702, 2007) reported that differential engagement of TIM-1 (KIM-1) during activation can positively or negatively costimulate T cell expansion and effector function. Xiao *et al* teach that crosslinking of Tim-1 by its ligand Tim-4 resulted in either activation or inhibition of T cell responses, thus raising the issue of whether Tim-1 can have a dual function as a costimulator. Xiao *et al* tested series of mAbs specific for Tim-1 and

identify two antibodies that showed *opposite functional effects*. One anti-Tim antibody *increased* the frequency of antigen-specific T cells, the production of the proinflammatory cytokines IFN-γ and IL-17, and the severity of experimental autoimmune encephalomyelitis (note that the claims are directed to treating an autoimmune disease). In contrast, another anti-Tim-1 antibody *inhibited* the generation of antigen-specific T cells, production of IFN-γ and IL-17, and development of autoimmunity, and it caused a strong Th2 response. Both antibodies bond to closely related epitopes in the IgV domain of the Tim-1 protein. Xiao *et al* concluded that the Tim-1 regulates T cell responses and that Tim-1 engagement can alter T cell function depending on the affinity/avidity with which it is engaged (see the abstract). Moreover, Umetsu *et al* (Nat Immunol. 2005;6(5):447-54) teach that *in vivo*, the use of antibody to TIM-1 plus antigen substantially *increased* production of interferon-γ in unpolarized T cells, prevented the development of respiratory tolerance, and increased pulmonary inflammation (see abstract). In fact, Umetsu *et al* reported that a TIM-1 specific Fab fragment, although capable of binding to TIM-1 does not have any T cell stimulatory effect (see page 450). Finally, the Examiner is directing Applicant's attention to US 2005/0276756 A1 which claims a method of *stimulating* an immune response in an individual, comprising administering anti-TIM-1 antibodies (see claims 23-25).

Thus, faced with contradictory and seemingly mutually exclusive function regarding the activity of the claimed antibody, undue experimentation would be required of the skilled artisan to determine the effect of anti-KIM-1 antibodies on autoimmune diseases such as IBD. Further, absent a positive correlation between anti-KIM-1 antibodies and IBD, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

The exemplification in the specification is drawn to inhibition of IFN-γ production *in vitro* (Example 11) by KIM-1-Ig and anti-KIM-1 antibodies and *in vivo* treatment with KIM-1-Ig fusion protein conferred significant protection to mice, as indicated by the improvement in the weight score and fewer blood present in the fecal pellets (Example 12 and fig. 14&15). While the specification uses "active immunization" with KIM-1-Ig to block IFN-γ production, the claims requires a "passive immunization" with an antibody to KIM-1. Given the teachings of Xiao *et al*, and Umetsu *et al* above, and importantly the teachings of Encinas *et al* (IDS reference AFF) that administration of anti-TIM-1 (KIM-1) antibody to mice (*in vivo*) has on effect on T_H1 cytokine IFN-γ production (see abstract). Moreover, Hoo et al (Clinical and experimental Immunology (2006), 145(1):123-129) teaches that administering anti-TIM-1 antibodies to a mice *enhances* interferon (IFN)-γ production (see abstract in particular). Administering such antibodies to a subject with an autoimmune disease, the antibodies either would not treat (Encinas *et al*) or would exacerbate (Hoo *et al*) the autoimmune disease including IBD in a subject. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *these* assays to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

11. Claims 42 and 46-47 are rejected under 35 U.S.C. 102(e) as being anticipated by US. Publication 2005/0014687.

The `687 publication teach a method of treating inflammation comprising administering antibodies to HAVcr-1 (KIM-1) protein to a patient in need thereof, wherein the inflammation associated with asthma, lupus and emphysema (see published claim 48 and ¶¶70 and 629 in particular), wherein the antibody is monoclonal or humanized antibody (see published claims 30 and 31 in particular).

The reference teachings anticipate the claimed invention.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 15, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644